REMARKS/ARGUMENTS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claim 1 has been amended to specify that the regulatory $CD4^+$ $CD25^+$ T cells are removed from human blood by "contacting human blood comprising $CD4^+$ $CD25^+$ T cells with ligands specifically binding to one or more members selected from the group consisting of the CD4, CD25 and CTLA-4 entities on the T cells." This language finds clear support in the instant specification at page 4, lines 27-28 ("utilizing agents/ligands specifically binding to the CD4, and/or CD25, and CTL-A4 (CD154) entities on the T cells.")

Claim 1 has also been amended to require a new step (c), requiring "identifying the $CD4^+$ $CD25^+$ T cells removed from the human blood in step (b) as $CD4^+$ $CD25^+$ regulatory T cells." This language finds clear support throughout the instant specification, and, indeed, was implicit in previous claim 12, which was drawn in part to "a method to ***identify*** * * * $CD4^+$ $CD25^+$ regulatory T cells from human blood."

Claim 25 has been amended to require that the "$CD4^+$ $CD25^+$ regulatory T cells are removed from the human ***peripheral*** blood." This language finds clear support in the instant specification at page 3, line 24.

Claims 28-32 have been amended to make what are believed to be only editorial changes.

New claim 33 is based, for example, on the disclosure at page 18, lines 24-28.

In short, Applicants do not believe that any of the changes to the claims introduce new matter. An early notice to that effect is earnestly solicited.

The sole issue for consideration is the final rejection of claims 12 and 24-32 under 35 USC § 103(a) as being obvious over Jonuleit et al. ("Jonuleit"), *J. Exp. Med., 192:* 1213-1222 (2000), in view of Takahashi et al. ("Takahashi"), *J. Exp. Med., 192:* 303-309 (2000). In response, Applicants respectfully submit that the cited combination of references fails to make out a *prima facie* case of obviousness against the instant claims.

In response to Applicants' previous arguments, the Examiner comments in the sentence bridging page 5-6 of the final rejection that

> "[T]he recited method steps do not include any step that would tell the difference between the cells being either memory cell or regulatory T cell, the claimed invention is simply drawn to a method that is able [to] isolate [a] T cell [that] expresses both CD4 and CD25."

Applicants respectfully submit that the Examiner's position on this point is untenable. Previous claim 28 already required that "said method further comprises the step of ***testing*** the $CD4^+CD25^+$ ***for a regulatory property*** of $CD4^+CD25^+$ T cells (emphasis added)." Previous claims 29-32 depended on claim 28, and further specified tests for particular regulatory properties. These test steps would differentiate the instant regulatory T cells from memory cells.

As noted above, all of the claims now include a differentiating step, as main claim 12 has been amended to require "identifying the $CD4^+$ $CD25^+$ regulatory T cells removed from the human blood in step (b) as $CD4^+$ $CD25^+$ regulatory T cells." New independent claim 33 also

includes such "identifying." The identification of the $CD4^{+}CD25^{+}$ T cells as ***regulatory*** $CD4^{+}CD25^{+}$ T cells clearly differentiates these $CD4^{+}CD25^{+}$ T cells from memory cells.

The Examiner focuses at the bottom of page 4 of the final rejection on the claimed method "comprising two ***simple*** steps." However, Applicants respectfully submit that there is no teaching or suggestion to make the claimed invention with a reasonable expectation of success in the combination of cited references and, therefore, the Examiner has not made out a *prima facie* case of obviousness irrespectively of the simplicity of the claimed method steps.

As stated in *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614, (Fed. Cir. 1999):

> "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. **Close adherence to this methodology is *especially* important in the case of less technologically complex inventions**, where the very ease with which the invention can be understood may prompt one 'to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against the teacher.'...**Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is *rigorous* application of the requirement for a showing of the teaching or motivation to combine prior art references**. [Emphasis added.]"

The Examiner says at the top of page 5 that "it would have been obvious to an ordinary artisan to try to identify whether such cells exist in human blood." However, Applicants respectfully point out once again that the art evidences ***the failure*** of persons skilled in the art to

isolate and correctly identify these regulatory T cells. Consequently, there is no basis for a finding that it would have been obvious to try the present invention with a reasonable expectation of success.

Moreover, Applicants believe the "obvious to try" standard should not be applied in the instant case. The Federal Circuit very recently in *Ortho McNeil Pharmaceuticals, Inc., v. Mylan Laboratories, Inc., et al.,* 86 USPQ2d 1196, 1201-1202 (Fed. Cir. 2008), confirmed that "a flexible TSM test ***remains*** the primary guarantor against a non-statutory hindsight analysis such as occurred in this case (emphasis added)." According to the Court, "[t]he TSM test, flexibly applied, merely assures that the obviousness test proceeds on the basis of *evidence*—teachings, suggestions (a tellingly broad term), or motivations (an equally broad term)—that arise before the time of invention as the statute requires (again, emphasis added)." *Id.* Consequently, a *prima facie* case of obviousness requires application of the flexible TSM test as opposed to an obvious-to-try approach.

The Examiner's proposed combination of Jonuleit and Takahashi simply does not teach or suggest the present invention, nor reveal to persons of ordinary skill in the art a reasonable expectation of success in carrying out the present invention. In the absence of such teaching or suggestion, or reasonable expectation of success, the combination of Jonuleit and Takahashi cannot make out a *prima facie* case of the obviousness of the instant claims.

The foregoing having been written, Applicants bring to the Examiner's attention in an information disclosure statement to be filed shortly references cited by the Japanese Patent Office in the corresponding Japanese patent application. Two of these references, abstracts by Ng et al. and Taams et al., purport to isolate human $CD4^+CD25^+$ regulatory T cells from human blood.

However, the abstracts provide no information exactly how these $CD4^+CD25^+$ regulatory T cells were isolated, and provide no actual data characterizing the $CD4^+CD25^+$ regulatory T cells allegedly isolated. Applicants respectfully submit, therefore, that these abstracts are insufficient, as a matter of law, to have placed the present invention in the possession of persons skilled in the art. Consequently, these abstracts do not stand as a bar to the grant of the instant claims.

Further on this point, Applicants respectfully remind the Examiner that cited references must be enabling ***to the same extent*** that the specification of the claimed invention must enable the claimed invention. Where references are not enabling, they are not citable as prior art, and no case of either anticipation or obviousness can be based on them. *See, In re Le Grice,* 133 USPQ 365, 374 (CCPA 1962):

> "[T]he proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought. [Emphasis added.]"

See also, In re Hoeksema, 158 USPQ 596, 601 (CCPA 1968), wherein the Court stated:

> "While In re Le Grice was bottomed on an issue arising under 35 U.S.C. 102 where the reference was a 'printed publication,' that test, in our view, is also properly applicable to issues arising under 35 U.S.C. 103."

Since the art had been unable to isolate and properly characterize these $CD4^+CD25^+$ regulatory T cells prior to the present invention, a person skilled in this art could not, in fact, take

the information in the two abstracts mentioned and combine this information with his or her knowledge and be put in possession of the present invention. Therefore, these two abstracts are nonenabling, and cannot serve as the basis for any anticipation or obviousness rejection against the present claims.

In view of the foregoing, Applicants respectfully submit that the Examiner would be fully justified to reconsider and allow this application. An early notice that this rejection has been reconsidered and withdrawn is, therefore, earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
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